## REMARKS

As an initial matter, Applicants gratefully acknowledge courtesies extended during a discussion with the Dr. Li on October 1, 2004 ("telephone discussion"). See the Office Communication dated October 8, 2004.

During that discussion, it was understood that the Office would view the response submitted on June 23, 2004 ("prior response") more favorably if Applicant provided further information about functional fragments of thrombomodulin (TM) and endothelial cell protein C receptor (EPCR). To comply, the information is provided and discussed below.

Also during the telephone discussion, the undersigned explained that a Notice of Appeal was filed on August 23, 2004 because the prior Office Action was marked "Final". Applicants appreciate notification from the Examiner that the finality of the prior Office Action was an error. See the Office Communication dated October 8, 2004.

However in a subsequent conversation, the Examiner indicated that it would be appreciated if Applicants submitted their amendments as part of an RCE submission. The Examiner also requested that a Petition For Time Extension and requisite fee be sent in that would extend the time from the two-month due date for filing the Appeal Brief (October 23, 2004) to January 23, 2005. The present submission complies with these requests.

During the telephone discussion, Dr. Li also indicated that claims to a combination therapy featuring TM, EPCR and particular administration vectors might be viewed favorably. New claims 52-55 (adenovirus vectors) and 56-58 (adeno-associated virus) are written along these lines.

It was also indicated that claims to a TM and EPCR combination therapy might be viewed favorably if further reference was made to expression level. New claims 59-67 are

written along those lines. In particular, new claims 59-67 now specify that the method includes an increase in activated protein C by about an order of magnitude versus a control.

Support for the present claim amendments can be found throughout the instant application including the drawings and claims as filed originally.

For instance, particular support for new claims 52-58 can be found on pg. 22, line 26 to pg 25, line 10; Examples 4-5, 9 (disclosing, for instance, construction and use of a recombinant adenovirus vector called AdTMh5); Example 7 (reporting construction and use of a recombinant adeno-associated virus vector called $AAV_2$ hTM). See also Figures 7A-B (outlining, for instance, construction of the vectors).

Additional support for new claims 59-67 can be found at pg. 26, lines 25-30. Support for "standard protein C assay" and related language in the claims can be found, for example, at pg. 19, lines 9-13. See also Figures 8B and 10 (showing, for instance, a rise in protein C activation following vector administration).

Support for the amendments to claims 29 and 30 to change "activation activity" to --binding activity-- is intended to address a typographical oversight.

No new matter has been added by virtue of the present claim amendments or new claims.

The following discussion is meant to supplement remarks made in the prior response.

**35 USC §112, first paragraph (written description and enablement)**

As pointed out in the prior Response, Applicants respectfully submit that they are in full compliance with §§ 112, first paragraph, particularly in view of the present claim amendments.

As requested by Dr. Li during the telephone discussion, Applicants provide additional evidence that one reading the instant disclosure would understand that a variety of functional TM and EPCR fragments could be used to practice the invention. To assure consideration by the Examiner, each reference is being submitted as part of a supplemental IDS (submitted with this paper).

1. Ref. AA Parkinson, JF et al. (*JBC* 265: 12602 (1990). The paper discloses stable expression of a secretable deletion mutant of recombinant human TM. Specifically provided is a construct (phd-TMD1) that encodes the extracellular domain of the TM but lacks transmembrane and cytoplasmic domains. The expressed deletion protein is said to have protein C activating activity.

2. Ref. AB Stearns DJ, et al. (*JBC* 264: 3352 (1989)). This reference reports that residues 310-486 of TM have protein C activating function. Importantly, the reference discloses specific TM fragments that have the activity (CB23) and those that do not (CB3). See Figure 1, for example, (summarizing TM domain organization).

3. Ref. AC Clarke JH et al. (*JBC* 268: 6309 (1993)). The Clarke paper reports that a methionine at position 388 is critical for activation of protein C. Oxidation of that amino acid is said to result in a loss of activity while substitution with Leu is reported to increase activity. The paper discloses a variety of single amino acid substitutions, deletions, and alanine insertional constructs within an interdomain loop (said to lie between EGF-like domains 4 and 5). Relationship between particular modifications (substitutions, deletions) and protein C activation is discussed. Various TM constructs were expressed in bacteria, insect and mammalian cells. See also Figure 1 (outlining important domain structures). See also Figure 2 (summarizing results of a study in which various portions of TM were mutagenized and analyzed for activity).

4. Ref. AD Kurosawa, S. et al. (*JBC* 263: 5993 (1988)). The paper discloses a 10 kDa fragment of thrombomodulin that activates protein C. See Figure 1 (disclosing the sequence of a particular cyanogen bromide fragment). See also Figure 5 (pointing to important EGF-like motifs in the TM protein).

5. Ref. AE Ye, J. et al. (*JBC* 267: 11023 (1992)). The Ye reference reports the making of three soluble TM fragments (ie., GF1-6, GF2.6-6, and GF5-6). Each fragment included specified amounts of repeated growth factor-like domains of the TM protein. Each fragment is reported to be able to activate protein C.

6. Ref. AF Kurosawa, S. et al. (*JBC* 262: 2206 (1987). This paper reports on various properties and functional domains of TM. In particular, limited protease digestions of the protein were made using trypsin and elastase. According to the authors, particular TM fragments activated protein C.

7. Ref AG Tsaing, M. et al. (*JBC* 267: 6164 (1992). The paper discloses specific structural requirements that are said to be needed for protein C activation, for instance. In particular, deletion of particular amino acid residues in certain EGF-like domains is said to hinder protein C activation. See Figure 1 (showing, for instance, a schematic representation of deletion mutants of human TM).

8. Ref AH Lin, JH et al. (JBC 269: 25021 (1994). The Lin reference provides various human TM constructs in which certain amino acids have been altered (eg., Ser 474). See Figure 1 (showing the structure and activity of various TM mutants).

9. Ref AI Fukudome, K. et al. (*JBC* 271: 17491 (1996)). This paper discloses a soluble form of EPCR that does not include its transmembrane domain. This truncated EPCR protein is

reported to activate protein C. Several other EPCR constructs were reportedly made. See Figure 6, for instance (showing activity of various EPCR cDNA constructs).

**10.** Ref AI Fukudome, K. and Esmon, CT (*JBC* 270: 5571 (1995) The paper reports the cloning and sequencing of various murine and bovine EPCRs. Comparisons between human, bovine and mouse forms of the protein are reported. All forms could bind activated protein C according to the reference.

**11.** Ref AI Xu, J. et al. (*JBC* 275: 6038 (2000)). The Xu paper also discloses a soluble form of EPCR that does not include its transmembrane domain. This truncated EPCR protein is reported to activate protein C.

**12.** Regan, LM et al. (*JBC* 272: 26279 (1997)) This reference also discloses a soluble form of EPCR that does not include its transmembrane domain. This truncated EPCR protein is reported to activate protein C.

This information is in line with the detailed disclosure provided by Applicants' specification.

For instance, and has been pointed out in a prior response, pg. 17, line 13 to pg. 19, line 25 of Applicants' specification describe a variety of suitable TM molecules (full-length and suitable fragments) for use with the invention.

Applicants' specification precisely defines the phrase "functional fragment" of TM at pg. 17, lines 26 to 30, for instance.

Additional full-length and function TM fragments for use with the claimed invention are described at pg. 18, lines 4-16 of the specification.

Still further TM molecules including functional fragments thereof are described at pg. 18, lines 18-28 for use with the claimed invention.

Appropriate full-length EPCR and functional fragments thereof are described at pg. 7, lines 24-30; pg. 8, lines 28-31; and pg. 10, lines 21-26 (referring also to Example 9).

Additional description of suitable full-length EPCR and functional fragments thereof can be found at pg. 20, lines 14-21 (providing reference to six scientific and patent references).

In view thereof, it is respectfully submitted that a worker reading the case would understand that the claimed invention could be used with a variety of TM and EPCR molecules including functional fragments thereof. A variety of such functional fragments were known as of the filing date (see rep 1-12, above, and the specification). Thus, there is no basis for the instant written description rejection. Moreover, the specification clearly satisfies the "how to make" and "how to use" requirements of § 112. Reconsideration and withdrawal of the rejection are requested.

**35 USC 103 (obviousness)**

During the telephone discussion, the Examiner confirmed the Office position that the claimed invention is obvious in view of references as cited in the outstanding office action. It was requested that Applicants delete reference in the claims 29 and 30 to a combination therapy using TM and EPCR. While Applicants respectfully disagree with the position taken, the concern has been addressed by this submission.

In particular, claims 29 and 30 now recite use of single agents with the proviso that when the agent is thrombomodulin that the nucleic acid further encode NF-κB inhibitor.

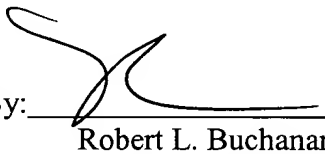
Respectfully, none of the references taken individually or together disclose or otherwise suggest the invention of claims 29 and 30.

In view thereof, reconsideration and withdrawal of the rejection are requested.

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this submission, the USPTO is authorized to charge our deposit account no. **04-1105** should such fee be deemed necessary.

Respectfully submitted,

Date: 11 JAN 05

By: 

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